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Two New Prenylated Stilbenes with an Irregular Sesquiterpenyl Side Chain from Propolis from Fiji Islands

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Abstract: Two new prenylated stilbenes with an irregular sesquiterpenyl side chain, solomonin B (**1**) and solomonin C (**2**), together with four known compounds, glyasperin A (**3**), isolated for the first time from propolis, kumatakenin (**4**), macarangin (**5**) and mangiferolic acid (**6**) were isolated from ethanol extract of propolis from Fiji islands. The compounds structures were determined based on their spectral data analysis (1D- and 2D NMR, UV and HREIMS) and comparison with literature data. The chemical composition of propolis from Fiji islands was determined for the first time.

Keywords: Fijian propolis; prenylated stilbenes; spectroscopic analyses; GC/MS.

1. Introduction

Propolis (bee glue) is one of the most valuable bee products with healing properties and natural source of biologically active compounds. Nowadays it is extensively used in complementary and alternative medicine, in food and beverages to improve health and prevent diseases such as inflammation, heart disease, diabetes and cancer [1]. It has been proven to possess wide range of biological activities (antimicrobial, antiviral, antioxidant, anti-inflammatory, anticancer, etc.), due to different propolis constituents such as polyphenols, terpenoids, steroids and amino acids [2, 3]. Unlike the biological activity, chemical composition of propolis is highly variable and depends mainly on the local flora, because in different habitats bees often choose different plant species as propolis sources [4]. Therefore, propolis from unexplored regions attracts the attention of scientists in the search for new bioactive molecules.

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In the past decade several reports have been published on the chemical composition and biological activity of propolis from some countries of the Pacific region. Its main constituents are prenylated flavonoids and cycloartane type triterpenes, originating from *Macaranga tanarius* and *Mangifera indica*, respectively [5-10]. But still no phytochemical studies have been previously reported for propolis from Fiji islands. Fijian propolis has recently been shown antimicrobial activity against isolates of diabetic foot ulcers [11]. In this article, we report our results on the constituents and plant sources of propolis from Fiji islands. Two new prenylated stilbenes with an irregular sesquiterpenyl side chain (**1**) and (**2**), together with four known compounds (**3**-**6**) were isolated and identified.

2. Materials and Methods

2.1. General

HREIMS spectra of the new compounds were recorded on Thermo Scientific Double- focusing High Resolution Magnetic Sector Mass spectrometer, in electron impact (EI) mode. UV-VIS spectra were taken in methanol with Helios Gamma Spectrophotometer. 1D- and 2D- NMR spectra were recorded on Bruker AVANCE II+ 600 NMR spectrometer operating at 600 MHz (150 MHz for ^{13}C) in DMSO-d_6 (deuterated dimethyl sulfoxide) with TMS as internal standard. The chemical shift values were reported in ppm (δ) units and the coupling constants (J) were given in Hz. Column and flash chromatography were performed on Silica gel 60 (Merck, 63-200 μm), normal phase. Preparative thin-layer chromatography (PTLC) was performed on Silica gel 60 F_{254} glass plates (Merck, 20 × 20 cm, 0.25 mm).

2.2. Propolis

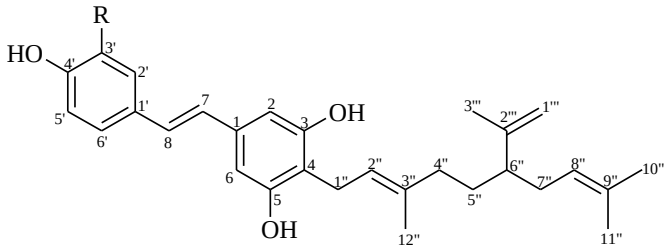
Propolis sample was collected in Tailevu Province, Viti Levu island, Fiji in April 2010, by scraping.

2.3. Extraction and Isolation

Crude propolis (73 g) was cut into small pieces and extracted three times with 70 % ethanol in water (1 : 10, w/v) at room temperature for 24 h. After filtration a small part of the combined 70 % ethanol extract (10 mL) was evaporated to dryness and subjected to gas-chromatography – mass spectrometry (GC-MS) analysis after silylation (5 mg of dry 70 % ethanol extract were mixed with 50 μl of dry (water-free) pyridine and 75 μl of BSTFA (bis(trimethylsilyl)-trifluoroacetamide) and heated at 80°C for 20 min). The GC/MS analysis was performed with a Hewlett– Packard gas chromatograph 5890 series II Plus linked to a Hewlett–Packard 5972 mass spectrometer system equipped with a 30 m long, 0.25 mm i.d., and 0.5 μm film thickness HP5-MS capillary column. The temperature was programmed from 60 to 300°C at a rate of 5°C/min, and a 10 min hold at 300°C. Helium was used as a carrier gas at a flow rate of 0.8 mL/min. The split ratio was 1:10, the injector temperature 280°C, the interface temperature 300°C, and the ionization voltage 70 eV. The remaining amount of the EtOH extract was concentrated under reduced pressure and extracted successively with light petroleum ether (PE, 40 – 60°C) and ethyl acetate (EtOAc) three times. The extracts obtained were evaporated to dryness and give 2.8 g and 5.6 g dry light petroleum and EtOAc extracts respectively.

The EtOAc extract (5.6 g) was subjected to silica gel flash chromatography (mobile phase methylene chloride/EtOAc 95 : 5 to 100 % EtOAc, v/v) and 18 fractions (*Fr.1- Fr.18*) were obtained. *Fr.3* (0.7 g) was rechromatographed on a silica gel column eluted with light petroleum/EtOAc (98 : 2 to 90 : 10, v/v) and 12 fractions (*Fr.3.1- Fr.3.12*) were obtained. Fractions *Fr.3.5* and *Fr.3.6* were combined (58 mg) and further were subjected to PTLC (silica gel, mobile phase chloroform/EtOAc 95

: 5 v/v, three- fold development) to yield **3** (8.6 mg). Recrystallization of *Fr.4* (0.8 g, from aceton) afforded compound **4** (12 mg) as yellow needles. The residue after recrystallization of **4** was further subjected to column chromatography (silica gel, mobile phase methylene chloride/EtOAc 95 : 5 to 85 : 15) to afford 7 fractions (*Fr.4.1- Fr.4.7*). *Fr.4.1* (19 mg) was further purified by PTLC (silica gel, mobile phase light petroleum/EtOAc 7 : 3, two-fold development) to yield **5** (2.4 mg). *Fr.4.2* (43 mg) was further purified by PTLC (silica gel, mobile phase chloroform/MeOH/H_2O 60 : 10 : 1) to yield **6** (5.2 mg). *Fr.4.4* (35 mg) was subjected to PTLC (silica gel, mobile phase chloroform/EtOAc 8 : 2) to yield **1** (3.5 mg) and **2** (1.5 mg).



1 R=OCH_3
2 R=H

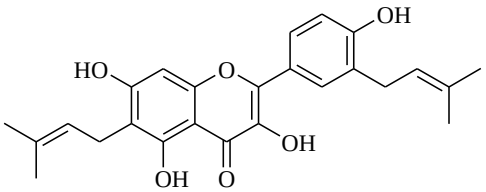


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Figure 1. The structures of compounds **1**-**3**.

Solomonin B **(1)**. Yellow resin; UV (MeOH) λ_{max} (log ε) 219 (4.35), 324 (4.24) nm; HREIMS *m/z* 462.27034 [M+] (calcd. for $C_{30}H_{38}O_4$, 462.27646); ^{1}H and ^{13}C NMR, ^{1}H-^{1}H COSY and HMBC data are shown in Table 2.

Solomonin C **(2)**. Yellow resin; UV (MeOH) λ_{max} (log ε) 219 (4.35), 325 (4.30) nm; HREIMS *m/z* 432.26559 [M+] (calcd. for $C_{29}H_{36}O_3$, 432.26590); ^{1}H and ^{13}C NMR data are shown in Table 2.

3. Results and Discussion

3.1. GC/MS analysis

The GC-MS analysis of the ethanol extract of Fijian propolis after silylation (Table 1) revealed the presence of typical metabolites for propolis from Pacific region, originating from *Mangifera indica*, which is one of its plant sources: mixture of alk(en)ylresorcinols, anacardic acids, cycloartane type triterpenes (cycloartenol, mangiferolic acid and their derivatives) [9, 10]. However the GC-MS profile demonstrated also the peaks of several major unknown compounds which mass spectra fragmentation corresponds to prenylated flavonols and stilbenes, which plant source is other than *Mangifera indica*. According to the literature stilbenoids are biologically active components, but not so common propolis components and only few have recently been isolated from propolis collected in Kenia, Kangaroo island (Australia), Solomon islands and Ghana [7, 12-14]. For this reason more detailed chemical studies of this propolis sample were performed.

Table 1. Chemical composition of ethanol extract of propolis from Fiji Island, according to GC/MS analysis (after silylation).

Compounds	% of TIC[a]	Compounds	% of TIC[a]
Alk(en)yl resorcinols	**3.6**	**Triterpenes**	**7.9**
Alkenyl resorcinol $C_{15:1}$	0.3	β-Amyrin	2.0
Alkyl resorcinol $C_{15:0}$	0.5	α-Amyrin	1.1
Alkenyl resorcinol $C_{17:2}$	0.7	Cycloartenol	1.9
Alkenyl resorcinol $C_{17:3}$	0.2	Lupeol	0.4
Alkenyl resorcinol $C_{17:1}$	1.3	20,24-Dammaradien-3-one	0.3
Alkenyl resorcinol $C_{19:1}$	0.6	Dipterocarpol	0.4
		Mangiferolic acid	1.8
Anacardic acids	**1.6**	Mangiferonic acid	tr.
$C_{15:1}$ side chain	0.1	Oleanolic acid	tr.
$C_{15:0}$ side chain	0.1		
$C_{17:2}$ side chain	0.1	**Aromatic acids**	**1.6**
$C_{17:1}$ side chain	0.7	Benzoic acid	tr.
$C_{19:1}$ side chain	0.6	p-Hydroxybenzoic acid	0.2
		Gallic acid	1.4
Flavonoids	**2.0**	Cinnamic acid	tr.
Kumatakenin	0.8	Caffeic acid	tr.
Kaempferol methyl ether	0.1		
Kaempferol	0.2	**Fatty acids**	**4.2**
Galangin	0.2	Palmitic acid ($C_{16:0}$)	2.8
Quercetin dimethyl ether	0.1	Palmitoleic acid ($C_{16:1}$)	tr.
Quercetin	0.6	Linoleic acid ($C_{18:2}$)	tr.
Luteolin	tr.	Oleic acid ($C_{18:1}$)	0.9
		Stearic acid ($C_{18:0}$)	0.3
Prenylflavonoids	**25.6**	15-Hydroxyhexadecanoic acid	tr.
Monoprenyl kaempferol	0.8	Isooleic acid ($C_{18:1}$)	0.2
Prenylflavonol	4.0	14-Hydroxyhexadecanoic acid	tr.
Prenylflavonol	19.4	Eicosanoic acid ($C_{20:0}$)	tr.
Prenylflavonol	1.2	Docosanoic acid ($C_{22:0}$)	tr.
Prenylflavanone	0.2	Tetracosanoic acid ($C_{24:0}$)	tr.
Prenylated stilbenes	**5.1**	**Others**	**6.3**
M=600	0.1	Ethyl amine	0.4
M=610	1.0	Glycerol	4.5
M=648	2.3	Hexadecanol	1.4
M=668	1.6	Dehydroabietic acid	tr.
M=668	0.1		
Sugars	**36.5**		

[a]The total ion current generated depends on characteristics of the compound concerned and is not a true quantification.

3.2. Structure elucidation

The EtOAc fraction of the ethanol extract of propolis from Fiji after repeated chromatographic procedures afforded two new prenylated *trans*-stilbenes with an irregular sesquiterpenyl side chain, solomonin B (**1**) and solomonin C (**2**), together with four known compounds, glyasperin A (**3**) [15], kumatakenin (**4**) [16], macarangin (**5**) [17] and mangiferolic acid (**6**) [18]. The known prenylated flavonol glyasperin A (**3**) (Figure 1) was isolated for the first time from propolis. All structures were determined based on the spectral data analysis and comparison with literature data.

Solomonin B (**1**) was isolated as yellow resin. Its HREIMS showed the molecular ion peak at *m/z* 462.27034 $[M]^+$, indicating the molecular formula of **1** as $C_{30}H_{38}O_4$ (calcd. 462.27646). This was supported by ^{13}C NMR analysis. The UV spectrum of **1** showed absorptions (λ_{max} 219 and 324 nm) typical for a stilbene chromophore. Proton signals in the ^1H NMR spectrum corresponding to a *trans*-vinyl group (two doublets, for one proton each, at δ 6.78 and 6.83 with J=16.2 Hz) supported the presence of a *trans*-stilbene structure in **1** [7]. Further analysis of the ^1H NMR spectrum in DMSO-d_6 (Table 2) revealed that the compound has *trans*-stilbene skeleton with both an AA' benzene ring system (singlet for two protons at δ 6.44, which corresponds to 1,3,4,5-four substituted benzene ring)

and an AMX benzene ring system (doublet at δ_H 6.74 (J=8.4 Hz), doublet of doublets at δ_H 6.92 (J=8.4; 1.8 Hz) and doublet at δ_H 7.15 (J=1.8 Hz), for one proton each, confirmed the presence of 1, 3, 4 three substituted benzene ring). The appearance of signals for four olefinic methyl groups (singlets at δ_H 1.53, 1.55, 1.61,and 1.67), three aliphatic methylene groups (multiplets at δ_H 1.35, 1.78 and 1.97), a benzylic methylene group (doublet for two protons at δ_H 3.16 with J=6.6 Hz), a CH proton (multiplet at δ_H 1.94), and two vinyl protons (multiplets at δ_H 4.98 and 5.15) along with two exomethylene protons (=CH_2, doublet and quartet at δ_H 4.60 and 4.69 respectively, for one proton each, which have HSQC correlation with signal at δ_C 111.3) pointed to the presence of a C_{15}- unit, connected to benzene ring. By ^{1}H-^{1}H COSY and the extensive analysis of HMBC (Table 2) the structure of the C_{15}- unit was determined as 3”,9”-dimethyl-6-(prop-1”’-en-2”’-yl)deca-2”,8”-dienyl. In the ^{13}C NMR the signals for four aromatic carbons connected with oxygen were observed (δ_C 146.4, 147.8 and 2x156.0). The presence of singlet for three protons at δ_H 3.82, which showed HSQC correlation with δ_C 55.6, along with the absence of additional signals in ^{1}H NMR spectrum confirmed the presence of one methoxy and three hydroxy groups. In the HMBC spectrum of **1**, the methylene signal at δ_H 3.16 (H-1”) was observed to correlate with C-3 (δ_C 156.0), C-4(δ_C 113.8) and C-5 (δ_C 156.0), indicating that the sesquiterpenyl group is attached to C-4. The methoxyl group is attached to C-3’ based on the HMBC correlation between the signal at δ_H 3.82 and C-3’ (δ_C 147.8). Thus, according to UV, HREIMS, 1D- and 2D NMR techniques (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H COSY, HSQC and HMBC) the compound **1** was determined to be 3’-methoxy-4-[3”,9”-dimethyl-6-(prop-1”’-en-2”’-yl)deca-2”,8”-dienyl]-*E*-resveratrol, a new prenylated *trans*- stilbene named solomonin B (Figure 1).

Solomonin C (**2**) was isolated as yellow resin with molecular formula of $C_{29}H_{36}O_3$ based on the HREIMS (*m/z* 432.26559 $[M]^+$, calcd. 432.26590). This was supported by ^{13}C NMR analysis. Its ^{1}H and ^{13}C NMR spectra were very similar to those of **1**. The major differences were the absence of the signals for methoxyl group at δ_H 3.82 and δ_C 55.6 in ^{1}H and ^{13}C NMR of **2** respectively. These observations, coupled with the presence of two doublets at δ_H 6.74 and 7.38, for two protons each, with J=8.7 and 8.6 Hz, respectively, in ^{1}H NMR of **2** (Table 2) confirmed that the second benzene ring of stilbene moiety is 1,4-disubstituted. The remaining signals in NMR spectra (^{1}H, ^{13}C, DEPT and HSQC) of **2** fully match those of the compound **1**. Based on these data and by comparison with spectral data of similar compound, reported in the literature [19] the compound **2** was determined to be 4-[3”,9”-dimethyl-6-(prop-1”’-en-2”’-yl)deca-2”,8”-dienyl]-*E*-resveratrol, a new prenylated *trans*-stilbene named solomonin C (Figure 1).

In nature the prenylated flavonols and stilbenes are typical components of *Macaranga* species [19-21]. The presence of such compounds in propolis from Fiji Islands suggests that the second plant source of Fijian propolis is a representative of genus *Macaranga*. It is well known that the prenylated stilbenes are biologically active components [12, 14, 20] and in this respect the biological activity of the new compounds requires further studies.

Table 2. NMR spectroscopic data for solomonin B (**1**) and solomonin C (**2**) in DMSO-d_6 (δ in ppm, *J* in Hz).

Position	Solomonin B (1)				Solomonin C (2)	
	^{1}H	^{13}C	HMBC (H→C)	^{1}H-^{1}H COSY	^{1}H	^{13}C
1		135.5(C)				135.7(C)
2	6.44 (2H, *s*)	104.2(CH)	3, 4, 5, 6, 7		6.43 (2H, s)	104.4(CH)
3		156.0(C)				156.3(C)
4		113.8(C)				114.0(C)
5		156.0(C)				156.3(C)
6	6.44 (2H, *s*)	104.2(CH)	2, 3, 4, 5, 7		6.43 (2H, s)	104.4(CH)
7	6.83 (1H, *d*, J=16.2)	125.9(CH)	2, 6, 1’	8	6.79 (1H, d, J=16.8)	126.0(CH)
8	6.78 (1H, *d*, J=16.2)	127.1(CH)	1, 7, 2’, 6’	7	6.76 (1H, d)*	127.3(CH)
1’		128.6(C)				128.5(C)
2’	7.15 (1H, d, J=1.8)	109.6(CH)	8, 4’, 6’	6’	7.38 (2H, d, J=8.6)	128.2(CH)
3’		147.8(C)			6.74 (2H, d, J=8.7)*	115.4(CH)
4’		146.4(C)				157.6(C)
5’	6.74 (1H, d, J=8.4)	115.5(CH)	1’, 3’	6’	6.74 (2H, d, J=8.7)*	115.4(CH)
6’	6.92 (1H, dd, J=8.4; 1.8)	120.0(CH)	8, 2’, 4’	2’, 5’	7.38 (2H, d, J=8.6)	128.2(CH)
1’’	3.16 (2H, d, J=6.6)	22.0(CH_2)	3, 4, 5, 2’’, 3’’	2’’	3.15 (2H, d, J=7.2)	22.4(CH_2)
2’’	5.15 (1H, m)	123.0(CH)	4’’, 12’’	1’’	5.14 (1H, m)	123.0(CH)
3’’		133.1(C)				133.4(C)
4’’	1.78 m	37.0(CH_2)	2’’, 3’’, 5’’, 12’’	5’’	1.79 m	37.4(CH_2)
5’’	1.35 m	30.5(CH_2)	4’’, 6’’	4’’	1.31 m 1.38 m	30.4(CH_2)
6’’	1.94 m	46.5(CH)	7’’	5’’	1.91 m	46.7(CH)
7’’	1.97 m	31.7(CH_2)	6’’, 8’’, 2’’’	8’’	1.93 m	32.1(CH_2)
8’’	4.98 (1H, m)	123.0(CH)		7’’	4.98 (1H, m)	123.3(CH)
9’’		131.0(C)				131.3(C)
10’’	1.53(3H, s)	17.7(CH_3)	8’’, 9’’, 11’’	8’’	1.53(3H, s)	18.3(CH_3)
11’’	1.61 (3H, s)	25.6(CH_3)	8’’, 9’’	8’’	1.61 (3H, s)	26.2(CH_3)
12’’	1.67 (3H, s)	16.0(CH_3)	2’’, 3’’, 4’’	2’’	1.67 (3H, s)	16.5(CH_3)
1’’’	4.60 (1H, d, J=2.4) 4.69 (1H, q, J=1.2)	111.3(CH_2)	6’’, 3’’’	1’’’, 3’’’	4.61 (1H, br. s) 4.69 (1H, br. s)	111.6(CH_2)
2’’’		147.2(C)				147.3(C)
3’’’	1.55 (3H, s)	18.4(CH_3)	6’’, 1’’’, 2’’’	1’’’	1.55 (3H, s)	18.6(CH_3)
OCH_3	3.82 (3H, s)	55.6(CH_3)	3’			

*Partially overlapped

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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